

Application No.: 10/587,498
Amendment and Response dated September 9, 2009
Reply to Final Office Action of March 11, 2009
Docket No.: 903-196 PCT/US/RCE
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Remarks/Arguments:

Introduction

Claims 20 and 21 have been added. Support for the newly added claims maybe found in the Specification at, *inter alia*, paragraphs [0012] and [0017].

No new matter is introduced with these amendments. Entry of the amendments is respectfully requested.

Section 102 Rejections

Claims 1-6, 8, 10, 12, 16, 17 and 19 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Kaupp, “Environmentally Protecting Reactive Milling” (hereinafter “Kaupp”). Applicants respectfully traverse.

As summarized by the Examiner, Kaupp et al. describes an experiment in which dichlorobenzene and tetrabutyltin are milled with quartz sand at 300 rpm and 100 rpm in an argon atmosphere at a speed of 14 m/s. Due to the treatment, Kaupp concluded that mineralization had taken place as the organic compound had disappeared.

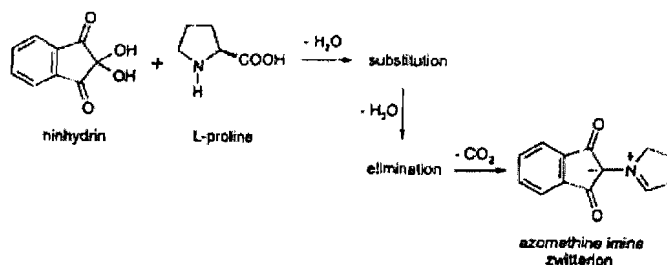
In the view of the office action, such mineralization between the organic and inorganic compound was asserted to be equated with a phase transformation for anticipation of at least claim 1.

It is clear, however, that there chemical reactions involved in Kaupp. Such chemical reactions are in direct contrast to the present invention. The present invention is directed to a phase transformation, where no chemical reaction takes place.

With regard to the chemical reactions of Kaupp, it is respectfully requested that the Examiner consider the section “Tribochemistry with Oxides” at page 5 of Kaupp. By splitting SiO_2 bonds, the freshly cleaved faces are unsaturated with free $|\text{Si}$ and $\text{O-Si}|$ radicals and other highly reactive species representing local plasma. Kaupp specifically teaches that such plasma tends to be saturated immediately. In other words, Kaupp teaches that chemical reactions result from it techniques. The tribochemistry of Kaupp is also described as useful for mineralization of compounds such as chlorinated aromatics or tin alkyls when milling is performed with sand to chemically change dangerous environmental poisons to benign compounds, again clear indications of chemical reactions in direct contrast to the present invention.

Moreover, at page 6, Kaupp specifically describes its milling of two different compounds, i.e., o-dichlorobenzene and tetrabutyltin. After milling Kaupp specifically states that “[m]ass spectrometric analysis of the solid powder [after milling] ... did not exhibit the starting material any more”. (Kaupp page 6). More specifically, only traces of o-dichlorobenzene were observed after milling, again clear indication of the mineralization of Kaupp being directed to chemical reactions in direct contrast to the present invention.

Still furthermore, Kaupp clearly shows chemical reactions with its milling of ninhydrin and L-proline at page 7. Here ninhydrin and L-proline are milled to chemically react to form azomethine imine zwitterion. Kaupp even provides the chemical formula for its chemical reaction, which is reproduced below for the convenience of the examiner, as follows:



Finally, Kaupp describes its milling as being useful for either high energy milling (HEM) or reactive milling (RM). (Kaupp, page 4. HEM is described by Kaupp as merely being a method for particle size reduction. (Kaupp, page 5). RM is described and specifically defined as including a chemical reaction. (*Id.*)

Thus, none of the definitions and none of the examples of Kaupp disclose the present invention, i.e., phase transformation of solid organic molecules achieved essentially by means of transmission of high kinetic energies.

Clearly, all claim limitations and claim words must be considered by the examiner. *In re Wilson*, 424 F.2d 1382, 1.85, 165 USPQ 4945, 496 (CCPA 1970), MPEP (8th Ed Revised July 2008) §2143.03. Moreover as Kaupp fails to disclose the claimed limitation of, *inter alia*, phase transformation of solid organic molecules achieved essentially by means of transmission of high kinetic energies, under the Section 102(b) rejection the Examiner must then properly apply an inherency argument to the missing descriptive matter of Kaupp. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Crown Oper. Int'l Inc. v. Solutia Inc.*, 289 F.3d 1367, 62 U.S.P.Q.2d 1917 (Fed. Cir. 2002). Further, inherency may not be established by probabilities or possibilities, and the mere fact that a certain thing may result from a given set of circumstances is not sufficient for a *prima facie* case of anticipation. *Scaltech Inc. v. Retec/Tetra L.L.C.*, 153 F.3d 1193, 51 U.S.P.Q.2d 1055 (Fed. Cir. 1999). Occasional results are not inherent. *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1365, 52 U.S.P.Q.2d 1303, 1306 (Fed. Cir. 1999). Clearly, the disclosure of Kaupp, especially considering its disclosure towards reactive milling with clear chemical reactions, does not rise to the level of being an anticipatory prior art reference.

Clearly, the Examiner must first present a *prima facie* case of anticipation to which the Applicant may then respond. The Examiner may not shift the burden under the Section 102

rejection to the Applicants to show “why the process of Kaupp cannot possibly do the same as the instant invention”, as indicated at page 2 of the Advisory Action. Such an attempt by the Examiner clearly runs afoul of the well established law for inherency.

Thus, the milling sand with organic compounds as disclosed by Kaupp results in a chemical reaction and not a phase transformation. Accordingly, Kaupp fails to disclose, explicitly or inherently, the present invention as presently defined by independent claims 1, 16 and 19.

For the record Kaupp is also considered by the Examiner to be relevant for, *inter alia*, current claim 6 (polymorph to polymorph transformation), claim 8 (transformation from a non-pure phase to a pure phase) and 19 (phase transition in a co-crystal) due to the description of the synthesis of an azomethine imine zwitterion from proline and ninhydrin which is regarded by the Examiner as a co-crystal (a multicomponent crystal). Here Kaupp, however, is not related to a phase transformation but is rather related to a tribochemical reaction. The reaction products in this case of Kaupp are, according to the reaction scheme the zwitterion and H₂O and CO₂. Such reaction products, however, are in direct contrast to the phase transformations of the present invention because such reaction products are indicative of, *inter alia*, chemical changes.

Furthermore, for the record it is respectfully submitted that Kaupp fails to provide a *prima facie* case of obviousness, i.e., Kaupp fails to teach or suggest the present invention. In KSR, the Supreme Court stated that “[o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine known elements in a fashion claimed by the patent at issue.” *KSR Int’l Co. v. Teleflex.*, 550 U.S. 398, 418, 127 S.Ct. 1727, 1740-41 (2007). The Court noted that “[t]o facilitate review, this analysis should be made explicit.” *Id.* (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.

2006)/("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.") *Id.* As Kaupp clearly teaches that its reactive milling results in chemical changes in contrast to phase transformations, Kaupp clearly fails to teach or suggest the present invention. In establishing a *prima facie* case of obviousness, the cited references must be considered for the entirety of their teachings. *Bausch & Lomb, Inc. v. Barnes-Hind, Inc.*, 230 U.S.P.Q. 416, 419 (Fed. Cir. 1986). It is impermissible during examination to pick and choose from a reference only so much that supports the alleged rejection. *Id.* Applicants respectfully submit that only through impermissible hindsight reconstruction may the Examiner attempt to reach the present invention through Kaupp. It is well established, however, that hindsight reconstruction of a reference does not present a *prima facie* case of obviousness, and any attempt at hindsight reconstruction using Appellants' disclosure is strictly prohibited. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1445-46 (Fed. Cir. 1993).

Thus, independent claims 1, 16 and 19, and all claims dependent therefrom, are patentably distinct over Kaupp. Therefore, reconsideration and withdrawal of the rejection of the claims over Kaupp are respectfully requested.

With respect to the objections raised in the Advisory Action regarding Kaupp, Kaupp is a clear example of "reactive milling" or tribochemical reactions. It is the intention of Kaupp that the components that are mixed together react with one another. The process disclosed in Kaupp involves the breaking and forming of atomic bonds.

A phase transformation is different. No atomic bonds are formed or broken. A phase transformation is a reorganization in the solid phase of otherwise intact molecules. In other words, during a phase transformation, the molecule remains the same, but its packing in the solid state changes. See in this respect also the application, page 9, as follows:

“[T]he process according to the invention influences the weak intermolecular interactions. These may, for example, be hydrogen bonds or further intermolecular interactions which are based on dipol-dipol or van der Waals interactions. Phase transformations shall be understood not to mean classic reactions or syntheses in which, for example, covalent bonds are broken and/or newly formed.” (emphasis added)

Kaupp discloses three specific examples of reactive milling, quartz with dichlorobenzene, quartz with tetrabutyltin and ninhydrin with proline.

In the first two examples, quartz with dichlorobenzene or tetrabutyltin, all dichlorobenzene or tetrabutyltin (starting material) is disappeared or at least reduced. In the third example, two components are combined of which it is known that they are reactive towards each other (last lines of the section on Organic Solid-State Syntheses reactions without Wastes), resulting in a zwitterion with H₂O and CO₂ as byproducts of the reaction. In all three examples, molecules are converted into other molecules (whatever they may be in the first two examples). In all three examples covalent bonds are broken and formed, indicating that the process is reactive milling or tribochemical reactions occur. In contrast, with the present invention no phase transformation occurs.

In the present application, and in particular from the examples and the drawings, it is clear that the same compound is converted into various solid forms while the molecular structure remains intact (no covalent bonds are formed or broken).

Again, Kaupp solely teaches reactions between molecules and not phase transformations. Kaupp teaches reactive milling between an organic (dichlorobenzene, tetrabutyltin) and an inorganic compound (quartz) or between two organic molecules of known reactivity towards each other.

One of ordinary skill in the art looking for ways to create phase transitions in solids would, when reading Kaupp, learn that such process conditions result in reactions between the components present. This would mean to him that the conditions employed in Kaupp would be such that degradation is also possible when solid organic molecules would be subjected to these process conditions. In fact, Kaupp already teaches this, as the reactive milling with quartz results in the degradation of the organic molecules (no useful product remains). He would therefore not be motivated to test the process conditions of Kaupp to create phase transformations. The only teaching of phase transformations is the subject application.

The inventors have basically found that high kinetic energy conditions may be employed for inducing phase transformations in solid organic molecules. This was unexpected as such conditions and the plasma formed in Kaupp would be expected to lead to degradation products due to the reactivity of the plasma.

Regarding the comment of the Examiner that "There is no statement that the chemical process of Kaupp is what does the phase transformation." Applicants do not understand this assertion by the Examiner. However, as explained above, the process of Kaupp that does not perform phase transformation. The process of Kaupp is reactive milling of two or more compounds together such that they react to a product that has a different molecular structure and solid form from the starting compounds.

The process of the present invention is non-reactive milling of organic molecules such that a phase transformation occurs to lead to a product that has the same molecular structure but a different solid form than the starting compounds.

Thus, Kaupp fails to disclose, reach or suggest the invention as presently defined by independent claims 1, 16 and 19. Reconsideration and withdrawal of the rejections of independent claims 1, 16 and 19, and all claims dependent therefrom, are respectfully requested.

Claim 18 was rejected under 35 U.S.C. §102(b) as allegedly being anticipated by US 2003/0113802 to Matzger et al. (hereinafter "Matzger"). Applicants respectfully traverse.

Matzger is considered by the office action to allegedly be relevant for the novelty of claim 18 (method for inducing phase transition by high kinetic energy milling or HKE milling) as it discloses the generation of polymorphs from drugs.

Matzger in [0030] merely describes that "polymorphism can exert profound effects on pharmaceutical processing, including, ..., milling, granulation and tableting".

It is respectfully submitted that the office action confuses HKE milling to induce phase transitions with the normal pharmaceutical processing (from powder to tablet), which may comprise milling as a technique, next to granulation etc. Moreover, Matzger specifically teaches formation of crystalline polymorphs by taking a sample of a dissolved compound and promoting crystal growth on two or more polymers. (See, Matzger, paragraph [0012]). Clearly, Matzger fails to disclose, teach or suggest the HKE method of claim 18.

Nevertheless, the Examiner alleges that milling speed and various parameters in Matzger could be easily controlled (and hence extended to accommodate the HKE milling of the present invention). The Examiner is not correct in this respect. With HKE milling, very high speeds and g-forces are applied, as described in the application. These parameters are clearly outside the scope of the conventional milling as disclosed in the relevant section of Matzger. It is respectfully submitted that to one of ordinary skill in the art, the disclosure of milling in Matzger vis-à-vis the HKE milling of the present invention are completely different processes.

When Matzger is read in the proper context by one of ordinary skill in the art, for instance by consulting some of the cited literature in [0030] it is clear that something else is intended in Matzger than what the Examiner alleges. The relevant paragraph [0030] describes that different polymorphs have different solid state properties. The different solid state

properties may have strong effects on pharmaceutical processing. The pharmaceutical processing is in this context exemplified as milling, granulation and tableting.

What this means is that when a compound exists in different solid forms (polymorphs), these different polymorphs may differ in their behavior in subsequent pharmaceutical processing, i.e., lead to tablets having different properties, essentially as argued before. Polymorphs as understood in the art and as described in Matzger represent different compositions of matter. (see, Matzger, paragraph [0017]). Thus, polymorphs are different materials of nature even though they may have an overall same chemical formula. For example, graphite and diamond have the same chemical formula, i.e., carbon, but are clearly different compositions of matter. (For the record, elements with different forms in nature are called allotropes, whereas polymorphs are directed to different materials from combinations of elements or compounds, for example, quartz and cristobalite are polymorphs of silica, i.e., silicon dioxide or SiO_2). This can also be derived from information obtainable from some of the cited references in the very same paragraph.

For instance in Otsuka et al., J Pharm. Science, 84:614 (1995), (copy of abstract enclosed) is described how the effect of environmental temperature on the compression mechanism of chlorpropamide (CPM) polymorph, forms A and C, was investigated. It was concluded that particle brittleness or plasticity was affected by compression at different temperatures. The higher tablet hardness of form A at 45°C was thought to be caused by the increased plasticity of primary particles, whereas that of form C at 45°C was ascribed to the decreased size of the secondary particles.

At least based on the abstract, no phase transformation is disclosed or taught through milling, let alone HKE milling.

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Tuladhar MD et al. in J Pharm Pharmacol 35, 269, 1982 (copy of abstract enclosed) described the dissolution rate of phenylbutazone from tablets using two polymorphic forms of the drug. During compression, the particle size change of the drug was affected by the nature of the diluent.

Again at least based on the abstract, no phase transformation is described or taught using HKE milling.

Also Wong and Mitchell in Int. J. Pharm., 88, 261, 1992, (copy enclosed) investigated the downstream processing of chlorpromazine hydrochloride and conclude that the different solid forms have different characteristics such as morphology, DSC, XRPD etc which have their effect on tableting. In this case, wet granulation introduced a phase change leading to different tableting behavior.

Once more, Matzger fails to disclose (explicitly or inherently), teach or suggest phase transformation using HKE milling.

Thus, Matzger fails to disclose, teach or suggest the invention as presently defined by independent claim 18. Reconsideration and withdrawal of the rejection of independent claim 18 is respectfully requested.

Section 103 Rejections

Claim 7 was rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kaupp in further view of Metzger. Applicants respectfully traverse.

As described above, Kaupp fails to teach or suggest the invention as presently defined by independent claim 1. Further, as described above, Metzger fails to teach or suggest the present invention, including, *inter alia*, high kinetic energy phase transformation.. Accordingly, Metzger

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fails to cure the deficiencies of Kaupp. Reconsideration and withdrawal of the rejection of claim 7 is respectfully requested.

Claims 11, 13 and 14 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kaupp. Applicants respectfully traverse.

As described above, Kaupp fails to teach or suggest the invention as presently defined by independent claim 1. Accordingly, reconsideration and withdrawal of the rejections of claim 11, 13 and 14 are respectfully requested.

Summary

Therefore, Applicants respectfully submit that independent claims 1, 16 and 18-21, and all claims dependent therefrom, are patentably distinct. This application is believed to be in condition for allowance. Favorable action thereon is therefore respectfully solicited.

Should the Examiner have any questions or comments concerning the above, the Examiner is respectfully invited to contact the undersigned attorney at the telephone number given below.

A claim fee of \$440.00 for the presentation of two additional independent claims, i.e., claims 20 and 21, has been previously paid on July 10, 2009. These claims, however, were not entered by the Examiner. Thus, no claim fee for excess independent claims is due at this time. Nevertheless, the Commissioner is hereby authorized to charge payment of any additional fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if

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any, under 37 C.F.R. § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

Respectfully submitted,

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